PATENT Docket No.: 1038-1160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Loosmore, et al.
Application No.	:	09/857,843
Filing Date	:	September 17,2001
Title	:	Multi-Component Vaccine Comprising At Least Two Antigens From Haemophilus influenzae To Protect Against Disease
Grp./AU	:	1645
Examiner	:	Ja-Na Hines

August 12, 2004

APPEAL BRIEF

Dear Sir:

Introduction

This Appeal Brief is submitted pursuant to applicant's appeal from a Final Rejection of claims 1-5, 25 and 27 dated December 31, 2002. A Notice of Appeal was filed on June 3, 2003.

A Notification of Non-Compliance with 37 CFR 1.192(c) was mailed Feburary 17, 2004 requiring Applicants to file in triplicate a complete new brief in compliance with 37 CFR 1.192(c). In particular, the notice stated that:

(1) "The brief does not contain a concise explanation of the claimed invention, referring to the specification by page and line number and to the drawings, if any, by reference characters (37 CFR 1.192(c)(5)); and

(2) "the brief includes the statement required by 37 CFR 1.192(c)(7) that one or more claims do not stand or fall together, yet does not present arguments in support thereof in the argument section of the brief."

Three copies of a new Appeal Brief are attached. Applicants believe the new Appeal Brief is in compliance with 37 CFR 1.192(c).

(1) **Real Party of Interest**

The real party of interest with respect to this patent application is Aventis Pasteur Limited. Assignments from the inventors to Aventis Pasteur Limited are recorded at Reel 013317/0711, 0724 and 0733 on September 20, 2002.

(2) **Related Appeals and Interferences**

The appellants, the appellants' legal representatives and assignee, are unaware of any pending appeals or interferences which will directly affect or be affected by or have a bearing on the Board's decision in the pending appeal.

(3) **Status of Claims**

This application was filed with claims 1-26. In the response dated September 25, 2002 to the Office Action of March 27, 2002 claims 6-24 and 26 were cancelled, claim 25 amended, and new claim 27 added.

Claims 1-5, 25 and 27 were finally rejected in an Office Action dated December 31, 2002. Claims 1-5, 25 and 27 are pending and the subject of this appeal and appear in Appendix I hereto.

(4) **Status of Amendments**

This application was filed with claims 1-26. Claims 1-5, 25 and 27 are pending and no amendments were filed subsequent to this final rejection.

(5) **Summary of Invention**

The present invention is directed to an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae,* including otitis media. The composition comprises at least two different antigens of *Haemophilus influenzae,* at least one of which antigens is an adhesin (page 4, lines 15-19; page 18, lines 3-12) and wherein said adhesin is a high molecular weight (HMW) protein of a non-typeable strain *of Haemophilus influenzae,* (page 4, lines 20-21; page 18, lines 3-12), particularly an HMW 1 or HMW 2 protein of the non-typeable strain (page 4, lines 21-22; page 5, lines 18-22; page 18, lines 3-12), and said antigen which is not an adhesin is a non-proteolytic heat shock protein of a strain of *Haemophilus influenzae* (page 4, lines 23-24; page 18, lines 3-12) and wherein the heat shock protein is an analog *of Haemophilus influenzae* Hin47 protein having a protease activity which is less than about 10% of that of the natural Hin47 protein (page 4, lines 24-27; page 18, lines 3-12). The invention is further directed to compositions where the HMW protein is recombinantly produced and said antigen which is not an adhesin is an analog of *Haemophilus influenzae* Hin47

protein having a decreased protease activity which is less than about 10% of that of the natural Hin47 protein in which the Histidine at amino acid position 91 is replaced by Alanine (page 5, lines 10-17; page 18, lines 3-12). The present invention is further directed to a method of immunizing a host against disease caused by infection with *H. influenzae* (page 7, lines 3-6; page 18, lines 13 to page 20, line 9 and Figures 1-6; page 20, lines 10-21 and Figures 7 and 8).

(6) **Issues**

The issues for consideration is the rejection of, claims 1-5 and 25 under 35 U.S.C. 112 1st paragraph and claims 1-5, 25 and 27 under U.S.C. 103(a) as being unpatentable over Barenkamp et al in view of Loosmore et al.

(7) **Argument**

(a) Background to the Invention

Haemophilus influenzae is the cause of several serious human diseases, such as meningitis, epiglottitis, septicemia and otitis media. There are six serotypes of *H. influenzae,* designated a to f, that are identified by their capsular polysaccharide. *H. influenzae* type b (Hib) was a major cause of bacterial meningitis until the introduction of several Hib conjugate vaccines in the 1980's. Vaccines based upon *H. influenzae* type b capsular polysaccharide conjugated to diphtheria toxoid, tetanus toxoid, or *Neisseria meningitidis* outer membrane protein have been effective in reducing *H. influenzae* type b-induced meningitis. The other serotypes of *H. influenzae* are associated with invasive disease at low frequencies, although there appears to be an increase in the incidence of disease caused by these strains as the incidence of Hib disease declines. Non-encapsulated or non-typeable *H. influenzae* (NTHi) are also responsible for a wide range of human diseases including otitis media, epiglottitis, pneumonia and tracheobronchitis. The incidence of NTHi induced disease has not been affected by the introduction of the Hib vaccines.

Otitis media is the most common illness of early childhood, with 60 to 70% of all children, of less than 2 years of age, experiencing between one and three ear infections. Chronic otitis media is responsible for hearing, speech and cognitive impairments in children. *H. influenzae* infections account for about 30% of the cases of acute otitis media and about 60% of chronic otitis media. In the United States alone, treatment of otitis media costs between 1 and 2 billion dollars per year for antibiotics and surgical procedures, such as tonsillectomies, adenoidectomies and insertion of tympanostomy tubes. It is estimated that an additional $30 billion is spent per annum on adjunct therapies, such as speech therapy and special education classes. Furthermore, many of the causative organisms of otitis media are becoming resistant to antibiotic treatment. An effective prophylactic

vaccine against otitis media is thus desirable.

(b) The Present Invention

Having regard to the above Background, it would be desirable to provide efficacious combination vaccines comprising *H. influenzae* components containing selected relative amounts of selected antigens. The present invention provides an immunogenic composition for conferring protection in a host against disease caused by infection with *H. influenzae*, including otitis media.

The immunogenic composition comprises at least two different antigens of *H. influenzae,* one of which is a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae* at least one of which is an adhesin as claimed in claim 1, and all claims dependant thereon.

Claim 2 recites that the adhesin is a high molecular weight (HMW) protein of a non-typeable strain of *H. influenzae.* Claim 3 recites that the HMW protein is a HMW 1 or HMW 2 protein of a non-typeable strain of *H. influenzae.* Claim 4 recites that the antigen which is not an adhesin is a non-proteolytic heat shock protein of a non-typeable strain of *H. influenzae.* Claim 5 recites that the heat shock protein is an analog *of Haemophilus influenzae* Hin47 protein having a protease activity which is less than about 10% of that of the natural Hin47 protein. Claim 27 further recites that the Hin47 protein having a decreased protease activity which is less than about 10% of that of the natural Hin47 protein in which the Histidine at amino acid position 91 is replaced by Alanine. The applicants data supports such results.

(c) Rejection of claims 1-5 and 25 under 35 U.S.C. 112 1st paragraph.

The HMW proteins are described in Barenkamp et al cited by the Examiner in the prior art rejection while the Hin47 analogs are described in the Loosmore et al reference cited by the Examiner in the prior art rejection. In the Barenkamp et al reference, there is described both the isolation of the HMW protein from natural-source materials and recombinant production. It is submitted, that the enablement is not limited to recombinantly-produced HMW protein.

In the Loosmore et al reference, there is described the manner of producing the non-proteolytic analog of Hin47 protein. In this respect, at least one amino acid contributing to protease activity is deleted or replaced by a different amino acid. The Loosmore et al reference describes how to identify such amino acid by comparison to known proteases. The reference specifically describes that the deleted or replaced amino acid may be selected from amino acids 195 to 201 and specifically describes replacement of Serine-197 with alanine, other specific amino acid mutations described are Histidine-91 replaced with alanine, and lysine or arginine-121 replaced with alanine. The immunogenic

properties of these various mutants are described in Loosmore et al. Based on this information, there is no reason to suppose that any other non-proteolytic analog would not also function in the same manner as the specific H9IA Hin47 analog utilized in the experiments described in the application (page 18 lines 4-12). It is submitted that enablement is not limited to the specific H91A Hin47 analog, but rather extends at least to any non-proteolytic analog of the Hin47 protein. The Examiner indicates that the objection of lack of enablement is based, to some extent, upon lack of guidance as to how to determine compositions other than that specifically identified by the Examiner. It is submitted that such is not the case.

Specifically, the specification tells a person skilled in the art that two different antigens of *Haemophilus influenzae* are employed and that one of them has to be an adhesin and the other does not. Testing to determine if an antigen is an adhesin or not an adhesin is within the skill of the art. In this regard, the Examiner's attention is directed to the experimentation described in Barenkamp.

In addition, the person skilled in the art is advised that one such adhesin protein is the HMW protein, where that is described and how to produce it both from natural-source materials and recombinantly (see page 2, line 23 to page 3, line 23). In addition, the person skilled in the art is advised that one such nonadhesin protein is a non-proteolytic analog of Hin47 protein or other non-proteolytic heat shock protein and how to produce such an analog (see page 3, line 14 to page 3 line 31).

Furthermore applicants have given guidance to one skilled in the art to test if a composition is an immunogenic composition (see example 4 pages 18 to 20 of the present application).

Having regard to the foregoing discussion, it is submitted that claims 1 to 5 and 25 are fully enabled by the disclosure.

(d) Rejection of claims 1-5, 25 and 27 under 35 USC 103(a).

Claims 1 to 5, 25 and 27 have been finally rejected under 35 USC 103(a) as being unpatentable over Barenkamp (WO 97/36914) in view of Loosmore et al (US Patent 5,506,139).

Claim 1 defines an immunogenic composition for conferring protection in a host against disease caused by *Haemophllus influenzae* comprising at least two different antigens of *Haemophilus influenzae*.

- one of which antigens is an adhesin
- the other of which antigens is not an adhesin.

The Examiner has identified Barenkamp et al as describing a *Haemophilus influenzae* protein which is an adhesin and Loosmore as describing a *Haemophllus influenzae* protein which is not an adhesin. The applicants position is that neither reference provides the motivation to combine the two immunogens in a single composition, as required by claim 1.

Barenkamp teaches high molecular weight proteins of non-typeable *H. influenzae* identified as HMW1, HMW2, HMW3 and HMW4, which are characterized by molecular weight and sequence information. Loosmore et al teach an analog of *H. influenzae* Hin47 protein with reduced protease activity. It is submitted that these references lack any motivation to combine two different antigens of *H. influenzae,* namely a non-proteolytic Hin47 protein of Loosmore e al with the HMW proteins of Barenkamp et al in an immunogenic composition. It is the applicants' position that neither reference provides the motivation to combine the two immunogens in a single composition as required by claim 1, and by dependency all claims on appeal.

While suggesting various combinations, there is no suggestion here to combine different proteins derived from the same pathogen, as in applicants' claim 1. Again, the references are silent as to any specific combination contemplated.

The cited prior art lacks the motivation to do so. There are vague, non-specified indications in both references to combine other components with the specific immunogen, but there is no specific indication as to what that other component may comprise, other than an adjuvant or materials from the pathogens and/or materials from various strains of the same pathogen.

As the Examiner has pointed out, on page 49, lines 15 to 19 of Barenkamp, it is stated:

> ".... the data suggests the HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multi-component NTHI vaccine."

This passage appears to suggest that only *Haemophilus* proteins which are the HMW adhesin proteins are appropriate components. The non-proteolytic analog of Hin47 is not an adhesin (although initially thought to be adhesin, see col. 2, line 17 of Loosmore et al). (It is pointed out that the Examiner is incorrect in the statement that the adhesin protein "should" comprises one component of the NTHI vaccine. As can be seen from the above quotation, Barenkamp uses the word "may").

Even if the Examiner finds motivation in this passage of Barenkamp to combine the HMW protein with another *Haemophilus* antigen, whether an adhesin or not, such motivation still provides no motivation to select the non-proteolytic Hin47 analog as the other *Haemophilus* antigen.

There have been a significant number *of Haemophilus* proteins identified as vaccine candidates besides the HMW and Hin47 analog proteins. These proteins include the various outer membrane proteins A to H, lactoferrin and transferrin receptor protein and the PI, P2, P6 and D15 proteins. It is submitted that there is no motivation provided by the cited prior art why a person skilled in the art would specifically select from all the optional possibilities, the non-proteolytic Hin47

analog to specifically combine with the HMW protein.

The Examiner states in the Office Action, quoting In re Kerkhoven, that:

> "The idea of combining them flows logically from their having been individually taught in the prior art."

The "idea of combining them" does not explain why the two materials should be combined when there is selection available. If the two antigens were the only two known antigens of *Haemophilus influenzae,* then there may be some validity to the position taken by the Examiner, but this is clearly not the case here.

In any event, caution is required when considering combining different antigens into immunogenic compositions because of the danger of impairment of the immunogenicity of the individual components one by the other. As may be seen from Applicants data, in Figure 3, immunogenic compositions are provided in which there is no impairment of individual antigenic components.

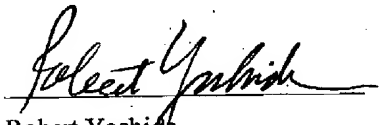
Furthermore, these results are unexpected in the field of combination vaccines. There is little expectation of success that simply mixing existing vaccine antigens will not result in incompatibilities amongst the various antigens, resulting in loss of stability or reduced potency or indeed a synergistic effect increasing potency. Immune interference cannot be predicted. Others skilled in the art of combination vaccines have found that the preparation of combination vaccines is far from straight forward. For example Cauldfield et al (2001) report on the need for a balanced formulations of vaccine components in the preparation of DTP combination vaccines to circumvent interference with the components. Van den Bosch et al (2003) have also reported that the addition of a potential antigen (Pal A) from *Actinobacillus pleuropneumoniae* can completely eliminate the positive efficacy of known antigens (Apxl and II) when combined (see abstract).

For all these reasons, it is submitted that claims 1 to 5, 25 and 27 are patentable over the applied art and the rejection thereof under 35 USC 103(a) as being unpatentable over Barenkamp in view of Loosmore et al. cannot be sustained.

Summary

Having regard to the above detailed discussion, it is submitted that the Examiner is in error in rejecting claim 1 to 5, 25 and 27 as being unpatentable under 35 USC 112 1st paragraph and the rejection under 35 USC 103(a) as being unpatentable over the combination of Barenkamp in view of Loosmore et al, should be REVERSED.

Respectfully submitted,



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